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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte MICHAEL R. BRISTOW, LESLIE A. LEINWAND, WAYNE MINOBE, and KOICHI NAKAO

Appeal 2008-0299
Application 09/558,472
Technology Center 1600

Decided: August 19, 2008

Before ERIC GRIMES, LORA M. GREEN, and RICHARD M. LEBOVITZ, *Administrative Patent Judges*.

GREEN, *Administrative Patent Judge*.

DECISION ON APPEAL

This is a decision on appeal under 35 U.S.C. § 134 from the Examiner's final rejection of claims 5-8 and 10. We have jurisdiction under 35 U.S.C. § 6(b).

STATEMENT OF THE CASE

There is only a single claim pending, claim 23, which is reproduced below.

23. A method of treating myocardial failure in a human comprising administering an effective amount of a transgene encoding for α-MHC, wherein expression of α-MHC provides improvement in left ventricular ejection fraction.

We reverse.

ISSUE

The Examiner contends that the Specification fails to enable the full scope of the method of claim 23.

Appellants contend that the enablement rejection is improper because the Specification, along with references submitted to support the enablement of the Specification, demonstrate that the claimed method is in fact enabled.

Therefore, the issue on appeal is: Are the Specification and the references submitted by Appellants sufficient to demonstrate that the method of claim 23 is enabled?

FACT FINDING

The Examiner rejected claim 23 under 35 U.S.C. § 112, first paragraph, on the grounds that the instant disclosure does not enable the full scope of the claimed subject matter (Answer 3).

The Examiner made the following findings with respect to the factors set out in *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988).[1]

The breadth of the claims: The Examiner notes that the claim reads on in vivo gene therapy, and "encompass[ ] administering a vector comprising a transgene or a naked transgene encoding for alpha-MHC to a human for treating myocardial failure via various administration routes so as to provide improvement in left ventricle ejection fraction." (Ans. 3.)

Nature of the invention and the state of the prior art: The Examiner notes that the invention is drawn to gene therapy, which was not well developed at the time of invention (Ans. 4).

The amount of direction or guidance presented and the existence of working examples: The Examiner states that the Specification discusses construction of the transgene, as well as modes of delivery of the transgene (Ans. 3). As to working examples, the Examiner notes that the Specification "shows that failing human left ventricle exhibited a significant reduction in alpha-MHC as compared to non-failing controls by RT-PCR analysis," as well as "up-regulation of alpha-MHC mRNA in myocardial tissue in human subjects suffering from idiopathic dilated cardiomyopathy, who received medical treatment with beta-blocking agent carvedilol or metoprolol." (Ans. 3.)

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[1] The factual considerations discussed in *Wands* are: (1) the quantity of experimentation necessary to practice the invention, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

According to the Examiner, however, the Specification "fails to provide adequate guidance for how to overcome . . . the . . . unpredictable parameters in the gene therapy art such that one would be able to achieve therapeutic alpha-MHC transgene expression in target cells in a human subject with myocardial failure." (Ans. 4.)

The Examiner notes further that the Specification "fails to provide a correlation to therapeutic levels of expression of alpha-MHC transgene in vivo in any subject having myocardial failure." (Ans. 6.) According to the Examiner, an increase in the amount of alpha-MHC transgene "does not provide a prediction of therapy for any subject having myocardial failure because of th[e] factors that complicate the unpredictability of gene therapy . . ., for example, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, the protein's compartmentalization within the cell, or its secretory fate, once produced, and the biological function of the protein." (*Id.*) Thus, the Examiner asserts, the Specification "fails to provide adequate guidance and evidence for a correlation between therapeutic levels of expression of alpha-MHC and improvement in the left ventricular ejection fraction in vivo." (*Id.* at 6-7.)

The relative skill of those in the art, the predictability or unpredictability of the art, and the quantity of experimentation necessary: The Examiner finds that gene therapy is highly unpredictable (Ans. 4). The Examiner cites Eck[2] as evidence of the state of the art (Ans. 4). Eck, the Examiner asserts, cites numerous factors that complicate gene therapy, such as the fate of the DNA

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[2] Eck, in Goodman & Gilman's The Pharmacological Basis of Therapeutics, McGraw-Hill, New York, pp. 77-101 (1996).

vector, consequences of altered gene expression and protein function, *etc.*, all of which differ dramatically based on the vector used, the protein being produced, and the disease being treated (Ans. 4).

The Examiner further cites Miller,[3] Deonarain,[4] Verma,[5] and Crystal[6] as evidence that "vector targeting to desired tissues in vivo continues to be unpredictable and insufficient." (Ans. 4-5.) As to cardiovascular gene therapy, the Examiner relies on Nabel[7] for its teaching that "myocardial gene therapy has been hindered by limited transfection efficiency, transient expression of recombinant genes, and vectors that have provoked inflammatory response." (Ans. 5-6.) Hajjar[8] is cited for its teaching that "relatively few vectors exist which achieve high-level transgene expression in post-mitotic cells, such as cardiomyocytes, and that these vector[s] evoke a robust immune response," thus "clinical applications will require other

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[3] Miller, *Targeted vectors for gene therapy,* 9 FASEB J. 190-199 (1995).
[4] Deonarain, *Ligand-targeted receptor-mediated vectors for gene delivery*, 8 EXP. OPIN. THER. PATENTS. 53-69 (1998).
[5] Verma, *Gene therapy-promises, problems and prospects*, 389 NATURE 239-242 (1997).
[6] Crystal, *Transfer of Genes to Humans: Early Lessons and Obstacles to Success*, 270 SCIENCE 404-410 (1995).
[7] Nabel, *Gene Therapy for Cardiovascular Disease*, 91 CIRCULATION 541-548 (1995), found at http://circ.ahajournals.org/cgi/content/full/91/2/541 (pagination in body of the opinion refers to the pagination from the reference obtained from the above online address).
[8] Hajjar, *Prospects for Gene Therapy for Heart Failure*, 86 CIRCULATION RESEARCH 616 (2000), found at http://circres.ahajournals.org/cgi/content/full/86/6/616 (pagination in body of the opinion refers to the pagination from the reference obtained from the above online address).

vectors or further refined vectors." (Ans. 6.) Hajjar is also cited for teaching that gene therapy "'has not yet proven its clinical value in any context,'" and that optimization into large animals and humans will require a large amount of further investigation (Ans. 6 (quoting Hajjar 2)).

The Examiner concludes:

> In view of the unpredictability of in vivo gene therapy in general, and particularly, unpredictability in myocardial gene therapy in vivo, and the lack of a correlation between therapeutic levels of expression of alpha-MHC and treatment of myocardial failure, such as improvement in the left ventricular ejection fraction in vivo, one skilled in the art at the time of the invention would not know how to treat myocardial failure in a human by administering a transgene encoding alpha-MHC such that expression of alpha-MHC would be able to provide therapeutic effect for treating said myocardial failure, such as improvement in left ventricular ejection fraction.

(Ans. 7.)

The Specification teaches that the transgene may be delivered by known methods, such as directly injecting naked DNA into the myocardium, through the use of a targeted vehicle, or through the use of a viral vector, of which an adenoviral vector is preferred (Spec. 16). According to the Specification, the "transgene is preferably infused directly into the heart by injecting it into the coronary artery, thereby ensuring the greatest amount of transgene absorption into myocytes." (*Id.*)

The Specification also demonstrates that treatment using β-adrenergic receptor blockade that resulted in improved left ventricular function showed an increase in the amount of α-MHC mRNA and a decrease in the amount of β-MHC (Spec. 37-38 (Example 5)). The Specification, however, provides

no working Example of the introduction of a transgene encoding for α-MHC into a human or an experimental animal model, wherein expression of α-MHC provides improvement in left ventricular ejection fraction.

James,[9] relied upon by Appellants to refute the Examiner's contention that the claimed method is not enabled by the Specification (App. Br. 4-5, referred to as the poster abstract from the lab of Jeffrey Robbins), discloses:

> The cardiac myosin heavy chain (MHC) isoforms, fast α-MHC and slow β-MHC, are expressed in developmental- and chamber-specific patterns. The mature human ventricle was thought to express only β, but recent reports show that healthy human ventricle contains ~2-10% α-MHC while diseased ventricle has only the β isoform. Because of the intrinsic functional differences between the two isoforms, it has been hypothesized that down-regulation of α-MHC is detrimental and contributes to the failing heart phenotype. Conversely, re-expression of α-MHC may be therapeutic for heart failure. Testing this hypothesis requires the ability to modulate α-MHC levels in an animal with a β-MHC ventricle. These experiments are now possible with the development of transgenic [TG] rabbits because the rabbit cardiac MHC expression pattern mimics human. We used the rabbit β-MHC promoter to drive expression of rabbit α-MHC in the heart and obtained four transgenic lines with varying proportions of ventricular α-MHC replacement ranging from ~10-15% (similar to basal human α-MHC levels) to ~50%. The TG animals appear outwardly normal with no difference in growth or longevity compared to NTG littermates up to age 24 months (the oldest rabbits currently available in our colony). . . . We have used these animals in pilot studies to test the hypothesis that persistent α-MHC expression will be protective during tachycardia induced

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[9] James, "Effects of Ventricular Expression of Alpha Myosin Heavy Chain in Transgenic Rabbits," Abstract presented at the Keystone Meeting on *Biology of Cardiac Disease* held on March 7, 2004.

> cardiomyopathy (TIC). After a 30 day pacing protocol with sequential increases in ventricular pacing rate, paced TG rabbits showed the expected increase in expression of α-MHC and decrease in β-MHC compared to NTG. Functionally, TG rabbits had a higher shortening fraction (24±2 vs. 20±3, TG vs. NTG, P=.016) and a higher VCFc (1.11±.12 vs. .78±.22, TG vs. NTG, P=.002). We conclude that persistent expression of α-MHC is protective during TIC.

(*Id.*)

PRINCIPLES OF LAW

"When rejecting a claim under the enablement requirement of section 112, the PTO bears an initial burden of setting forth a reasonable explanation as to why it believes that the scope of protection provided by that claim is not adequately enabled by the description of the invention provided in the specification of the application." *In re Wright*, 999 F.2d 1557, 1561-62 (Fed. Cir. 1993).

"[T]o be enabling, the specification . . . must teach those skilled in the art how to make and use *the full scope of the claimed invention* without 'undue experimentation.'" *Id.* at 1561 (emphasis added), *quoted in Genentech, Inc. v. Novo Nordisk A/S,* 108 F.3d 1361, 1365 (Fed. Cir. 1997). Thus, "there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed." *In re Vaeck*, 947 F.2d 488, 496 & n. 23 (Fed. Cir. 1991), *quoted in Enzo Biochem, Inc. v. Calgene, Inc.,* 188 F.3d 1362, 1374 (Fed. Cir. 1999). Some experimentation, even a considerable amount, is not "undue" if, e.g., it is merely routine, or if the

specification provides a reasonable amount of guidance as to the direction in which the experimentation should proceed. *See In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988).

ANALYSIS

The Examiner's rejection primarily focuses on the unpredictability of gene therapy in general. But the references relied upon by the Examiner specific to the use of gene therapy for heart failure do not support the Examiner's finding that gene therapy is inherently unpredictable and therefore not enabled in the absence of a working, therapeutic model.

First, as noted by the Federal Circuit, "[u]sefulness[10] in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans." *In re Brana*, 51 F.3d. 1560, 1568 (Fed. Cir. 1995).

Second, the Examiner relies on Nabel and Hajjar as teaching the unpredictability of cardiac gene therapy, thus providing evidence that the claimed method is not enabled. Those references, however, do not support the Examiner's conclusion that the nature of gene therapy of cardiac failure is inherently extremely unpredictable, such that more is required by Appellants' Specification to demonstrate enablement.

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[10] Although the Federal Circuit speaks in the terms of "usefulness," the rejection before the court was an enablement rejection based on the requirements of 35 U.S.C. § 112, first paragraph. *Brana*, 51 F.3d at 1568.

Nabel, as noted by the Examiner (Ans. 5-6), teaches:

> The field of cardiovascular gene transfer has developed rapidly during the past 5 years. Important advances have been made in vector development, in vivo gene delivery, and definition of potential therapeutic targets. Despite substantial progress, a number of technical issues need to be addressed before gene therapy is applied safely and broadly to cardiovascular diseases.

(Nabel 1 of 17.)

Nabel teaches further, however, that "[i]nitial studies demonstrated the feasibility of expression of reporter genes in rat and canine myocardium by direct injection of plasmid DNA," and that higher levels of expression have been obtained in rat myocardium after direct injection of adenovirus vectors (*id.* at 8 of 17). Nabel also teaches that "[a]dult myocardium in vivo has also been transduced by intravascular administration of adenoviral vectors encoding reporter genes." (*Id.*)

Hajjar, as noted by the Examiner (Ans. 6), teaches:

> The possibility of gene therapy for heart failure merits consideration at this time because of improvements in vector technology; cardiac gene delivery; and, most importantly, our understanding of the molecular pathogenesis of heart failure. . . . However, bridging the gap between these basic investigative studies and clinical gene therapy remains a formidable task. Early experiments in rodents will need to be extended to large-animal models with clinical-grade vectors and delivery systems to assess both efficacy and safety.

(Hajjar 1 of 12.)

Hajjar also teaches that "[i]ntracoronary catheter delivery of an adenovirus encoding β-galactosidase achieved transduction of ≈30% of the

myocytes in the distribution of the coronary artery" (*Id.* at 3 of 12). The authors also reported a catheter based technique in rodents, in which diffuse cardiac gene transfer was achieved *in vivo*, and note that other investigators have obtained similar results in other animal models (*id.*)

Nabel and Hajjar demonstrate that workers in the field have achieved successful gene transfer in animal models. The references, thus, at most evidence that further research and development is needed before routine clinical use in humans. As noted by the *Brana* court, however, that is not the standard by which enablement is measured.

Finally, the Specification (*see, e.g.,* Spec. 37-38 Example 5) and the results reported by Robbins, demonstrate that an increase in expression of α-MHC has an effect on ventricular function. The Examiner discounts the James abstract, stating:

> Although both the gene used in the Abstract and the instant invention are alpha-MHC, however, constantly expressing alpha-MHC at 10-15% to about 50% in a transgenic rabbit to be protective during TIC, as taught in the Abstract by James, is totally different from the claimed method of the instant invention, i.e. administering a transgene encoding alpha-MHC to a human via various administration routes so as to provide therapeutic effect for treating myocardial failure, such as improvement in left ventricular ejection fraction. In the transgenic rabbit, the alpha-MHC gene into [sic, goes into?] the genome of every cell in said rabbit and about 10-15% to about 50% of alpha-MHC is expressed in the heart cells. However, the instant invention requires administration of a transgene encoding alpha-MHC to a human via various administration routes and it is unclear whether sufficient transgene can reach the target cells, i.e. heart cells, and whether sufficient alpha-MHC protein can be expressed and obtained in sufficient duration of time so as to provide therapeutic effect for treating

> myocardial failure, such as improvement in left ventricular ejection fraction.

(Ans. 8.)

The abstract of James, however, demonstrates in a rabbit model that increased levels of α-MHC are protective. The Examiner fails to provide a reasonable basis to doubt Appellant's assertions in the Specification, and thus does not meet the burden of showing that the claimed invention lacks enablement. The Examiner's concerns are therefore reduced to the unpredictability of gene therapy, which, again, as discussed above, is not sufficient to support the enablement rejection.

CONCLUSIONS OF LAW

For the reasons set forth above, we conclude that the Specification and the references submitted by Appellants are sufficient to rebut the Examiner's enablement rejection, and the enablement rejection of claim 23 is therefore reversed.

REVERSED

cdc

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